Krajowa Konferencja Zastosowań Matematyki w Biologii i Medycynie

Sandomierz, 5th–9th September 2016

HAHNFELDT'S ET AL. MODEL ADAPTED FOR HETEROGENEOUS TUMOURS

Piotr Bajger[1], **Mariusz Bodzioch**[2]

[1]Inter-Faculty Individual Doctoral Studies in Natural Sciences and Mathematics
University of Warsaw
ul. Banacha 2c, 02-097 Warsaw
[2]Faculty of Mathematics and Computer Science
University of Warmia and Mazury in Olsztyn
ul. Słoneczna 54, 10-710 Olsztyn
[1]p.bajger@uw.edu.pl, [2]mariusz.bodzioch@matman.uwm.edu.pl

ABSTRACT

A modification of the Hahnfeldt et al. model of tumour growth under angiogenesis is proposed in this study. The tumour cell population is subdivided into two compartments which are then considered as competing species. Basic mathematical properties of the model are investigated.

INTRODUCTION

Angiogenesis is a process in which new blood vessels sprout from the existing vasculature. Without additional blood supply tumour growth is limited by the amount of nutrients available through diffusion. Emergence of new blood vessels also provides tumour cells with a direct access to the bloodstream and facilitates metastasis. The onset of angiogenesis hence often marks a transition from a benign mass to a malignant cancer. This may have disastrous consequences for the host. Much attention has been therefore paid towards a development of antiangiogenic therapy aimed to destroy the tumour's vasculature and limit its growth. [3]

As a basis for our study we take the Hahnfeldt et al. [1] angiogenesis model. This model is widely accepted and its parameters are well-fitted to the experimental data. In this model the growth of tumour under angiogenesis stimulation/inhibition is represented by the following system of two non-linear differential equations

$$\begin{aligned} \dot{V}(t) &= -\lambda V(t) \ln \frac{V(t)}{K(t)}, \\ \dot{K}(t) &= -\mu K(t) + bV(t) - dK(t)V^{2/3}(t), \end{aligned} \tag{1}$$

where $V(t)$ represents the tumour volume at time t, and $K(t)$ is the time-varying carrying capacity.

In this model Hahnfeldt et al. assumed that the tumour growth is governed by the Gompertz-type equation with carrying capacity related to the size of the tumour vasculature. Therefore the resulting equation for $V(t)$ is the Gompertz equation with the time-dependent carrying capacity $K(t)$. Moreover, the dynamics of $K(t)$ depends on the stimulation process initiated by poorly nourished tumour cells (here $bV(t)$), vessels loss due to the accumulation of the inhibiting factors

secreted by tumour cells ($-dK(t)V^{2/3}(t)$) and natural endothelial cell death ($-\mu K(t)$). It should be noted that the exponent $2/3$ present in the second equation represents the ratio of the tumour surface to its volume.

MODEL

We propose a modification of the model (1) in which we subdivided the cell population into two classes (e.g. resistant and sensitive to the potential treatment [2]) and considered them as competing species. Rather than focusing on the mutations from one class to another, we will focus on explicit competition between cells belonging to different classes. This is why we first proposed a "pure competition" model which ignores the mutations. The result is the following system of three ordinary differential equations (time dependence of the variables K, V_1, V_2 was omitted for clarity):

$$\begin{aligned} \dot{V}_1 &= -\lambda_1 V_1 \ln\left(\frac{\alpha_{11}V_1 + \alpha_{12}V_2}{K}\right), \\ \dot{V}_2 &= -\lambda_2 V_2 \ln\left(\frac{\alpha_{21}V_1 + \alpha_{22}V_2}{K}\right), \\ \dot{K} &= -\mu K + (b_1 V_1 + b_2 V_2) - d\,(V_1 + V_2)^{2/3}\,K, \end{aligned} \tag{2}$$

where $\alpha_{ii} = 1$, $i = 1, 2$, and α_{ij}, $i \neq j$, are the competition coefficients between the different types of tumour cells.

A potential application of such subdivision includes the modelling of acquired chemotherapy resistance. Explicit competition between tumour cells has, to the best of our knowledge, never been considered in the literature. However, in order to gain some insight into the dynamics and properties of this system, we focus on unperturbed tumour growth in the absence of therapy.

MATHEMATICAL PROPERTIES

We will investigate basic mathematical properties of (2), in line with the analogous findings regarding the original model (1), as obtained in [4]. We restrict our attention to the set

$$I = \{(V_1, V_2, K) \in (\mathbb{R}^+)^3\},$$

which is physically relevant.

We firstly note, that the right-hand side vector field associated with (2) is of class C^∞ in I, therefore Picard-Lindelöf Theorem yields local uniqueness and existence of solutions with given initial conditions.

Proposition 1. *The set I is invariant for the system (2).*

Proof. The equation for the volume of cells of type $i = 1, 2$ is equivalent to the integral equation

$$V_i(t) = V_i(0) \exp\left(-\lambda_i \int_0^t \frac{\alpha_{i1}V_1(s) + \alpha_{i2}V_2(s)}{K(s)} ds\right),$$

which is non-negative, provided that $V_1(0), V_2(0) \geq 0$.

For $K = 0$ we have $\dot{K} = b_1 V_1 + b_2 V_2 \geq 0$, since b_1, b_2 and V_1, V_2 are all non-negative. □

Proposition 2. *The solution to the system (2) through $\underline{x} \in I$ exists for all $t \geq 0$.*

Proof. From the inequality

$$-\ln x \leq \frac{1}{x} - 1 \text{ for } x > 0$$

it follows that for $i = 1, 2$

$$\begin{aligned}\dot{V}_i &\leq \lambda_i V_i \left(\frac{K}{\alpha_{i1} V_1 + \alpha_{i2} V_2} - 1 \right) \\ &\leq \lambda_i K \frac{V_i}{\alpha_{i1} V_1 + \alpha_{i2} V_2} \\ &\leq \lambda_i K,\end{aligned}$$

where we used non-negativity of V_1, V_2 and positivity of the parameters α_{ij} $(i, j = 1, 2)$.

From the equation for the carrying capacity, using non-negativity of V_1, V_2 and K

$$\dot{K} \leq b_1 V_1 + b_2 V_2 \leq \max\{b_1, b_2\}(V_1 + V_2).$$

It follows that

$$\frac{d}{dt}\left(V_1 + V_2 + K\right) \leq m\left(V_1 + V_2 + K\right),$$

where $m = \max\{b_1, b_2, \lambda_1, \lambda_2\}$. Hence

$$V_1 + V_2 + K = O(e^{mt}) \text{ for } t \geq 0$$

and the solution exists for all $t \geq 0$. □

STEADY STATES AND STABILITY

Now we will investigate the stability of the steady states of the system (2). It is easy to show that the system (2) has at most three steady states.

The first two steady states are semi-positive and correspond to the domination of one type of cells over the other. Let $S^{1*} = (V_1^{1*}, 0, K^{1*})$ denote the coordinates of the first steady state in which the first cell type dominates, where

$$V_1^{1*} = K^{1*} = \left(\frac{b_1 - \mu}{d} \right)^{3/2}.$$

It is easy to notice that the steady state S^{1*} exists provided that $b_1 > \mu$. By direct calculations it can be verified that the steady state S^{1*} is stable if $\alpha_{21} > 1$ and unstable if $\alpha_{21} < 1$.

By symmetry, the steady state $S^{2*} = (0, V_2^{2*}, K^{2*})$ exists if $b_2 > \mu$ with

$$V_2^{2*} = K^{2*} = \left(\frac{b_2 - \mu}{d} \right)^{3/2}.$$

The steady state S^{2*} is stable provided $\alpha_{12} > 1$ and unstable provided $\alpha_{12} < 1$.

The third steady state $S^{3*} = (V_1^{3*}, V_2^{3*}, K^{3*})$, at which both cell types coexist, exists provided that

$$\alpha_{12} < 1, \tag{3a}$$

$$\alpha_{21} < 1, \tag{3b}$$

$$b_1(1 - \alpha_{12}) + b_2(1 - \alpha_{21}) > \mu(1 - \alpha_{12}\alpha_{21}), \tag{3c}$$

and has the following coordinates

$$\begin{aligned}V_1^{3*} &= \frac{1 - \alpha_{12}}{1 - \alpha_{12}\alpha_{21}} K^{3*}, \\ V_2^{3*} &= \frac{1 - \alpha_{21}}{1 - \alpha_{12}\alpha_{21}} K^{3*}, \\ K^{3*} &= \frac{\Big(b_1(1 - \alpha_{12}) + b_2(1 - \alpha_{21}) - \mu(1 - \alpha_{12}\alpha_{21})\Big)^{3/2}}{d^{3/2}(1 - \alpha_{12}\alpha_{21})^{1/2}(2 - \alpha_{12} - \alpha_{21})}.\end{aligned}$$

Proposition 3. *If*

$$\lambda_1(b_2 - b_1\alpha_{12}) + \lambda_2(b_1 - b_2\alpha_{21}) > 0, \tag{4}$$

then the steady state S^{3*} is stable.

Proof. The Jacobian at the steady state S^{3*} is

$$J(S^{3*}) = \begin{bmatrix} \frac{b_1(1-\alpha_{12})+b_2(1-\alpha_{21})}{1-\alpha_{12}\alpha_{21}} & b_1 - \frac{2}{3}\sigma & b_2 - \frac{2}{3}\sigma \\ \lambda_1\frac{1-\alpha_{12}}{1-\alpha_{12}\alpha_{21}} & -\lambda_1\frac{1-\alpha_{12}}{1-\alpha_{12}\alpha_{21}} & -\lambda_1\alpha_{12}\frac{1-\alpha_{12}}{1-\alpha_{12}\alpha_{21}} \\ \lambda_2\frac{1-\alpha_{21}}{1-\alpha_{12}\alpha_{21}} & -\lambda_2\alpha_{21}\frac{1-\alpha_{21}}{1-\alpha_{12}\alpha_{21}} & -\lambda_2\frac{1-\alpha_{21}}{1-\alpha_{12}\alpha_{21}} \end{bmatrix},$$

where

$$\sigma = \frac{b_1(1-\alpha_{12}) + b_2(1-\alpha_{21}) - \mu(1-\alpha_{12}\alpha_{21})}{2-\alpha_{12}-\alpha_{21}} > 0,$$

by (3).

Let $p(x) = x^3 + a_2x^2 + a_1x + a_0$ denote the characteristic polynomial of the Jacobian J. We will show that $a_2, a_1, a_0 > 0$ and $a_2a_1 > a_0$, and use the Routh-Hurwitz stability criterion to show that all roots of p have a negative real part.

We have

$$a_2 = \frac{b_1(1-\alpha_{12}) + b_2(1-\alpha_{21}) + \lambda_1(1-\alpha_{12}) + \lambda_2(1-\alpha_{21})}{1-\alpha_{12}\alpha_{21}} > 0,$$

due to the condition (3).

Moreover

$$\begin{aligned} a_1 =& \frac{(1-\alpha_{12})(1-\alpha_{21})}{(1-\alpha_{12}\alpha_{21})}\left[\lambda_1(b_2 - b_1\alpha_{12}) + \lambda_2(b_1 - b_2\alpha_{21})\right] , \\ &+ \lambda_1\lambda_2\frac{(1-\alpha_{12})(1-\alpha_{21})}{1-\alpha_{12}\alpha_{21}} + \frac{2}{3}\sigma\frac{\lambda_1(1-\alpha_{12}) + \lambda_2(1-\alpha_{21})}{1-\alpha_{12}\alpha_{21}} , \\ >&0 \end{aligned}$$

because of the conditions (3) and the assumption (4).

We also have

$$a_0 = \frac{2}{3}\sigma(1-\alpha_{12})(1-\alpha_{21})\lambda_1\lambda_2\frac{2-\alpha_{12}\alpha_{21}}{(1-\alpha_{12}\alpha_{21})^2} > 0.$$

Finally, assuming again (4), we estimate

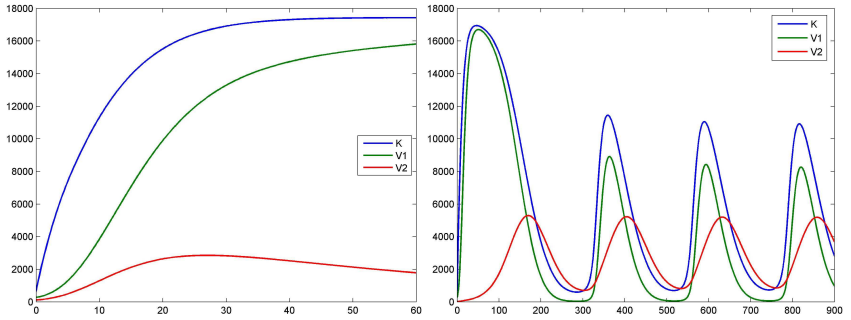
$$\begin{aligned} a_2a_1 >& \frac{2}{3}\sigma\frac{\Big(\lambda_1(1-\alpha_{12}) + \lambda_2(1-\alpha_{21})\Big)^2}{(1-\alpha_{12}\alpha_{21})^2} , \\ >& \frac{2}{2-\alpha_{12}-\alpha_{21}}a_0 , \\ >& a_0. \end{aligned}$$

The Routh-Hurwitz stability criterion therefore applies. □

Furthermore, we note that if the cells proliferate at the same rate ($\lambda_1 = \lambda_2$) or they secrete the proangiogenic factors at the same rate ($b_1 = b_2$), then the condition (4) is satisfied and S^{3*} is stable, whenever it exists.

Now we describe the link between the stability and existence of the states S^{1*}, S^{2*} and S^{3*}. Suppose that the steady states S^{1*} and S^{2*} exist and are unstable. Note that conditions (3a) and (3b) are satisfied and that we may estimate

$$\begin{aligned} b_1(1-\alpha_{12}) + b_2(1-\alpha_{21}) &> \mu(1-\alpha_{12}+1-\alpha_{21}) \\ &= \mu\Big((1-\alpha_{12})(1-\alpha_{21}) + (1-\alpha_{12}\alpha_{21})\Big) \\ &> \mu(1-\alpha_{12}\alpha_{21}), \end{aligned}$$



(a) (b)

Figure 1. Numerical solutions to the system (2): (a) the values of the relevant parameters are as in Table 1, $\alpha_{12} = 0.8$, $\alpha_{21} = 1.1$; (b) the values of the relevant parameters are as follows: $\lambda_2 = 0.042$, $b_2 = 0.30$, $\alpha_{12} = 0.7$, $\alpha_{21} = 0.4$. The other parameters are as in Table 1.

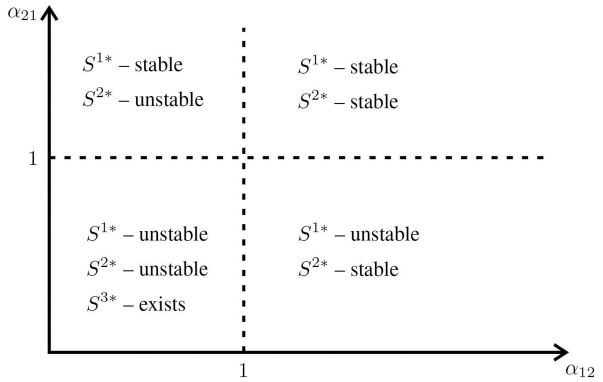


Figure 2. Bifurcation diagram for the system (2). For $\alpha_{12}, \alpha_{21} < 1$ the steady state S^{3*} exists and is stable provided that (4).

so that the condition (3c) is satisfied and the steady state S^{3*} exists.

We therefore conclude that the $(\alpha_{12}, \alpha_{21})$ parameter subspace is divided into four regions such that crossing from one region to another changes the stability of at least one steady state. These results are summarised in Figure 2.

It is important to note that although the positive steady state S^{3*} exists (see Figure 2), it may be unstable. For example, under certain choice of parameters system (2) exhibits oscillatory behaviour, as shown in Figure 1b.

DISCUSSION

A modification to the model proposed by Hahnfeldt et al. in (1999) [1] is proposed in this study. The modification introduces heterogeneity of the tumour cells with a potential aim to model the chemotherapy resistance. Explicit competition between different types of cells is considered in the absence of therapy. The problem is shown to be well-posed and the stability of the steady states was examined.

The model proposed has so far ignored mutations. This is because the initial aim was to formulate a "pure" system of equations to isolate the mechanism of competition and study it on its own. A next step in the model development would be to include mutations and conduct sensitivity analysis in order to determine the sensitivity to the parameters responsible for these two processes.

Name	λ_1	λ_2	μ	b_1	b_2	d
Unit	1/day	1/day	1/day	1/day	1/day	$\text{day}^{-1}\text{vol}^{-2/3}$
Value	0.192	0.192	0	5.85	5.85	0.00873

Table 1. Parameters for the model. The values of parameters $\lambda_1, \lambda_2, \mu, b_1, b_2, d$ are taken from [1]. The values of α_{12} and α_{21} were varied.

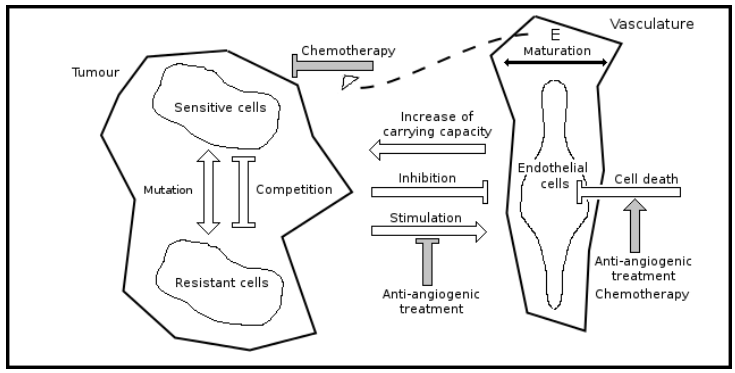


Figure 3. Schematic diagram of the interactions between different components of the final model. Grey arrows denote possible treatment targets.

This study is the first step in the development of a full model which incorporates two processes crucial from the point of view of effective chemotherapy planning – varying drug resistance and angiogenesis. Figure 3 shows a scheme of all the interactions which are to be included in the final version of the model.

By introducing treatment into the model it will be then possible to identify the mechanism responsible for the process of acquired drug resistance. Such an analysis will significantly improve our understanding of the behaviour of tumours and their response to chemotherapy.

ACKNOWLEDGEMENTS

Mariusz Bodzioch was partially supported by WCMCS, Warsaw, within PhD Internships programme.

REFERENCES

[1] P. Hahnfeldt, D. Panigrahy, J. Folkman, and L. Hlatky: *Tumor Development under Angiogenic Signaling: A Dynamical Theory of Tumor Growth, Treatment Response, and Postvascular Dormancy*, Cancer Research **59** (1999), 4770-4775.

[2] A. Świerniak: *Control problems related to three compartmental model of combined anticancer therapy*, Proceedings of the 20th Mediterranean Conference on Control & Automation, 2012.

[3] L. Pecorino: *Molecular Biology of Cancer: Mechanisms, Targets, and Therapeutics*, OUP, 2012.

[4] J. Poleszczuk and I. Skrzypczak: *Tumor Angiogenesis Model With Variable Vessels' Effectiveness*, Applicationes Mathematicae **38** (2011), 33-49.